Tercica

August 22, 2005

Lester M. Crawford, D.V.M., Ph.D.
Commissioner, Food and Drug Administration
c/o Division of Dockets Management
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Response to Citizen Petition of Insmed Incorporated
Docket No. 2005P-0322

Dear Commissioner Crawford:

We are writing in response to the above-referenced citizen petition submitted by Insmed Incorporated on August 11, 2005, requesting that the Food and Drug Administration (FDA) immediately deny approval of the pending new drug application (NDA) for a pioneer drug product known as Increlex™ (mecasermin [rDNA origin] injection).

Tercica, Inc. is the sponsor of Increlex™, an orphan-designated drug intended for the long-term treatment of growth failure in children with a severe form of primary insulin-like growth factor-1 (IGF-1) deficiency (severe Primary IGFD).[1] Insmed hopes to obtain FDA approval to market its own version of the drug, known as SomatoKine® (mecasermin [rDNA origin] rinfabate injection). Both products are currently under review at the agency. The expected action date for the Increlex™ NDA is August 31, 2005; the expected action date for the SomatoKine™ NDA is October 3, 2005.

By all appearances, Insmed's petition is nothing more than a ploy to delay a final decision on Tercica's NDA. The petition, submitted at the eleventh hour, is baseless. It consists of simplistic points that have long ago been addressed by Tercica, in consultation with the agency's Division of Metabolic and Endocrine Drug Products (DMEDP). It also includes a series of speculative and misguided attempts to question the quantity and quality of Tercica's data, all of which are easily rebutted. Most important, the petition offers no new evidence or argument that would justify the extraordinary request – at this late date – to immediately deny approval of the NDA.

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[1] Increlex™ is the subject of NDA No. 21-839, submitted to FDA on February 28, 2005. It is designated as an orphan drug (Orphan No. 95-0936) and has been assigned a six-month priority review under the agency's Prescription Drug User Fee Act program.

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The Insmed petition not only lacks merit, it lacks facial validity. It focuses primarily on the use of "compassionate use" data,[2] as if Insmed had surfaced the issue for the first time, and as if the NDA were devoid of any other data. This and related points were carefully considered by Tercica and its predecessor, Genentech, Inc., in close consultation with DMEDP. The clinical record in support of Increlex™ is, we believe, the most extensive collection of safety and efficacy data compiled for an IGF-1 product. It represents more than a decade of study with over 230 treatment-years of exposure.[3] Moreover, the data from our long-term, investigator-sponsored study add valuable supportive information on the safety of Increlex™. There is no reason to discount or disregard this data set, as Insmed suggests. Nor is there reason to believe that it represents the sole evidence in favor of approval.

Simply put, the safety of Increlex™ is fully characterized and amply demonstrated. In particular, the record shows that the risk of hypoglycemia presented by Increlex™ is well understood, manageable, and thoroughly outweighed by the expected therapeutic benefits. Finally, the proposed indication for Increlex™ properly defines the intended patient population by taking into account the heterogeneous molecular defects that cause severe Primary IGFD, as well as the evolving definitions of the relevant disease populations.

Given the lack of evidentiary support and other fatal defects in the petition, as discussed in detail below, we urge FDA to act on the petition on or before August 31, 2005. A swift response will blunt Insmed's abusive use of the petition process and promote the needs of the children who stand to benefit from Increlex™.

I. INCRELEX™

Increlex™ is a proposed drug product that consists of a recombinant human IGF-1 (rhIGF-1) in aqueous solution for the long-term treatment of growth failure in children with severe Primary IGFD. Primary IGFD is a disease

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2 "Compassionate use" is Insmed's term. More appropriately, our NDA includes data from several investigator-sponsored studies, including a long-term investigator-sponsored study.

3 *See generally* Tercica 2004 Annual Report, SEC Form 10-K (March 24, 2005), available at http://investor.tercica.com.

characterized by lack of sufficient IGF-1 production in the presence of normal or elevated endogenous growth hormone.[4]

If approved, Increlex™ will represent a breakthrough in the treatment of short stature in Primary IGFD patients. It will be the first FDA-approved product based on the IGF-1 protein, one of the principal molecular structures needed to support normal rates of statural growth in children. Endogenous IGF-1 plays a crucial role in stimulating multiple processes leading to statural growth, and also plays an important role in the acquisition and maintenance of bone mass. The metabolic actions of IGF-1 cause the cellular uptake of glucose, fatty acids, and amino acids and are key to the stimulation of cell, tissue, organ, and skeletal growth.

Increlex™ seeks to replicate the naturally occurring form of IGF-1, providing patients who are IGF-1 deficient with a viable replacement source for the protein. When administered in twice-daily doses, Increlex™ has been shown to cause statistically significant increases ($p<0.001$) in long-term growth rates. In one analysis, children ranging from two to ten years old experienced, on average, a three-fold increase in the rate of growth in the first year of therapy and a two-fold increase in growth rate over an eight-year period. Compared to pre-treatment growth patterns, the children gained, on average, an additional one inch per year for each year of therapy during the eight-year period.[5]

As discussed in detail below, the product is supported by an extensive safety database that includes clinical data collected over a ten-year study period. The product is also supported by a comprehensive non-clinical safety database. The most common adverse events associated with the product were hypoglycemia, injection site lipohypertrophy, and tonsillar hypertrophy.[6] All of these side effects are well characterized by the clinical data, their biological bases are well understood, and they are readily manageable through patient and physician labeling and physician oversight. In our studies in subjects with severe Primary IGFD to date, no patient has required withdrawal from a study because of an adverse event.

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[4] Approximately 6,000 children – whose height and IGF-1 levels are at least three standard deviations below normal – suffer from severe Primary IGFD. Tercica Press Release (May 2, 2005), attached at Tab 1.

[5] Tercica Press Release (June 16, 2004), attached at Tab 2.

[6] Tercica Press Release at Tab 1.

II. ANALYSIS

The Insmed petition makes three broad-based assertions about the pending NDA for Increlex™. None of Insmed's arguments is new, evidence-based, or compelling.

First, Insmed alleges that Tercica is relying primarily on data from a so-called "compassionate use program" and that such data are *per se* insufficient to establish the safety of Increlex™. Petition at 6-8. Along these lines, Insmed conjures up several other reasons why the NDA *may* contain data that are, according to Insmed, "highly suspect." Petition at 9-10.

Second, Insmed claims that Increlex™ presents an unreasonable risk of harm, particularly with respect to hypoglycemia and combined with the product's proposed twice-daily dosing. According to Insmed, rhIGF-1 products in general have a documented history of unacceptable risk and, therefore, irrespective of what Tercica has presented in the NDA, the product must be considered unsafe. Petition at 11-14. Put another way, according to Insmed, the evidence in the NDA must be suspect if it demonstrates that Increlex™ is safe.

Third, Insmed asserts that data from studies in patients diagnosed with Growth Hormone Insensitivity Syndrome (GHIS) cannot support the safety of rhIGF-1 in patients with severe Primary IGFD. Petition at 14-15. Insmed offers no affirmative proof or evidence as to why this must be so. Rather, Insmed relies on a single statement from Tercica on the evolving nomenclature in the diagnosis of the disease to support the claim. Petition at 14-15.

A. Increlex™ Is Supported by Robust Safety Data

The Increlex™ NDA contains robust data with which to characterize and establish the safety of the drug. Contrary to Insmed's assertions, the application consists of far more than a retrospective analysis of data from a "compassionate use" program. Petition at 8.

The Increlex™ NDA is based on a clinical development program initiated in the early 1990s by Genentech, after consultation with DMEDP on the size and number of studies that would be expected for registration; the intended patient population and enrollment criteria; the duration of the studies and the need for ongoing follow-up; and potential safety issues and safety endpoints. Based on early consultations with DMEDP beginning in 1991, Genentech initiated three Phase III studies (one blinded and two open-label) with enrollment numbers commensurate with the limited number of patients available for study.

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Genentech also monitored an investigator-sponsored study that offered yet another source of safety data.

Finally, existing patients from the Genentech program as well as more than 40 new patients who had begun rhIGF-1 therapy under investigator-sponsored studies were enrolled into a single long-term, open-label study (Study 1419), which has been continued by Tercica. This study is, we believe, the largest (in terms of number of patients) and deepest (in terms of duration of treatment) rhIGF-1 study in severe Primary IGFD patients available worldwide.

In particular, Study 1419 includes subjects whose exposure to the drug dates back to the first Genentech studies. To date, over 70 patients have been treated, half of whom have been dosed for 3.5 or more years. Some have been treated continuously for over 11 years. Given the limited size of the patient population available for study, this represents an extraordinary amount of clinical data. Moreover, with respect to safety, we note that no subject has had to withdraw from Study 1419 due to an adverse event.[7]

In early 2003, Tercica met with DMEDP to review the results of the Genentech Phase III studies, along with Tercica's plan for adding substantially to the existing data set. To support the findings of the Genentech studies, FDA requested that patients from Study 1419 be included in the NDA safety and efficacy analysis.

Thus, we believe there is no support for Insmed's broadside claim that international, multi-center, investigator-sponsored studies may not be used to support the safety of drug products. Petition at 6-7. This is especially true in the orphan drug context in children, where ethical considerations and the limited number of subjects with a given disease make randomized, controlled trials difficult. In this case, the Increlex™ NDA is supported by the original Genentech studies which, alone, may have been sufficient to establish the safety and efficacy of the drug. In addition, Tercica has been able to add a significant amount of safety data, collected across multiple centers, for an unprecedented number of severe Primary IGFD patients.[8]

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[7] Tercica Press Release at Tab 2.

[8] In addition, the safety of Increlex™ is supported by published literature and experience with rhIGF-1 therapy in several non-statural indications. *See, e.g.*, C. Azcona, *et al.*, *Growth Response to rhIGF-I 80 µg/kg Twice Daily in Children with Growth Hormone Insensitivity Syndrome: Relationship to Severity of Clinical Phenotype*, CLIN. ENDOCRINOL. 51: 787-92 (1999), attached at Tab 3; M.B. Ranke, *et al.*, *Insulin-Like Growth Factor I Improves Height in Growth Hormone Insensitivity: Two Years' Results*, HORMONE RES. 44: 253-64 (1995), attached at Tab 4; J. Guevara-Aguirre, *et al.*, *A Randomized, Double Blind, Placebo-Controlled Trial on Safety and Efficacy of Recombinant Human Insulin-Like Growth Factor-I in Children with*

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B. The Risk Profile of Increlex™ is Well Characterized and Manageable

1. The Risk of Hypoglycemia Has Been Addressed

Insmed has suggested, without offering any scientific evidence, four reasons why Increlex™ presents an unreasonable risk of hypoglycemia to patients.

First, Insmed takes issue with the product's twice-daily dosing regimen. Insmed argues that such dosing can be expected to result in twice as many falls in blood glucose per day, which may be symptomatic and result in serious adverse events. Petition at 12-14. In fact, the dosing regimen of Increlex™ was chosen expressly to *reduce* the risk of hypoglycemia, among other reasons. When comparing a twice-daily regimen to a once-daily regimen of equal total daily doses of rhIGF-1, the twice-daily regimen presents less risk of hypoglycemia, because of the reduced hypoglycemic potential of each dose.

Second, Insmed presents a false analogy between rhIGF-1 and insulin. Insmed states that a higher risk of hypoglycemia has been observed after three or more injections per day of insulin. Petition at 12-13. Obviously, insulin is a different drug than rhIGF-1, used in the treatment of a different disease (Diabetes Mellitus). And while it is true that rhIGF-1 has insulin-like effects, the relative blood glucose-lowering potency of rhIGF-1 is less than 10% compared to insulin.[9]

Third, Insmed makes an unfounded assumption regarding the administration of "free rhIGF-1." Insmed argues that "[t]he risk of hypoglycemia with twice daily administration of free rhIGF-1 is a clear safety signal that may carry unacceptable risks." Petition at 13. The term "free rhIGF-1," however, is misleading. As used by Insmed, it suggests (incorrectly) that rhIGF-1 monotherapy necessarily leads to excess unbound IGF-1 in the body, and that the administration of bound rhIGF-1 avoids this problem. In fact, after administration, the majority of rhIGF-1 binds to IGF binding proteins and is retained in the blood before being delivered to the tissues.[10] Insmed's self-

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Growth Hormone Receptor Deficiency, J. CLIN. ENDOCRINOL. METAB. 80: 1393-98 (1995), attached at Tab 5.

[9] *See* S.D. Boulware, *et al.*, *Comparison of the Metabolic Effects of Recombinant Human Insulin-like Growth Factor-I and Insulin: Dose-Response Relationships in Healthy Young and Middle-aged Adults*, J. CLIN. INVEST. 93(3): 1131-9 (1994), attached at Tab 6.

[10] Insmed cites two articles for the proposition that hypoglycemia is associated with exogenous rhIGF-1 administration. Petition at 5 n.10. Neither is relevant: In their study,

interested complaints about "free rhIGF-1" and "unacceptable risks" have no merit.

Fourth, according to Insmed, hypoglycemia from rhIGF-1 products is not likely to be managed or controlled by conventional measures. Petition at 11-14. Putting aside the lack of evidentiary support for this claim, it is important to recognize that instances of hypoglycemia in Tercica's studies were generally mild to moderate. Well accepted measures such as having subjects eat shortly before or after taking rhIGF-1, glucose monitoring, and withholding doses if the child is not eating, have been used successfully in rhIGF-1 studies to minimize hypoglycemia.

Tercica has worked with FDA to address the expected and well understood risk of hypoglycemia. Any such risk is manageable and clearly outweighed by the product's breakthrough therapeutic benefit for children with severe Primary IGFD.[11]

2. The Risk of Other Adverse Events Has Been Addressed

Throughout its petition, Insmed cites to adverse event rates for rhIGF-1 treatment from the published literature, in an attempt to demonstrate inconsistencies between these data and Tercica's data. Where the rates appear to differ from those reported publicly by Tercica, Insmed concludes that Tercica has under-reported or failed to adequately collect the data. Petition at 8-12. Once again, Insmed's arguments fail under scrutiny.

First, in Table 1 of the petition, Insmed compares the rates of tonsillectomy/adenoidectomy and intracranial hypertension in the then-65

H.P. Guler, *et al.*, used an intravenous route of administration, rather than the subcutaneous route proposed for Increlex™. H.P. Guler, *et al.*, *Short-Term Metabolic Effects of Recombinant Human Insulin-Like Growth Factor I in Healthy Adults*, N ENGL. J. MED. 317(3): 137-40 (1987), attached at Tab 7. In S.M. Firth, *et al.*, the route of administration was also intravenous and the subjects were rats rather than humans. S.M. Firth, *et al.*, *Impaired Blockade of Insulin-Like Growth Factor I (IGF-I)-Induced Hypoglycemia by IGF Binding Protein-3 Analog with Reduced Ternary Complex-Forming Ability*, ENDOCRINOLOGY 143(5): 1669-76 (2002), attached at Tab 8.

[11] With respect to the risk of hypoglycemia, Insmed also misquotes the literature. Insmed alleges that in a placebo-controlled study of rhIGF-1 conducted by Guevera-Aguirre, none of the placebo patients experienced hypoglycemia. Petition at 11. In fact, six hypoglycemic events occurred in *both* the rhIGF-1 (n=7) *and* placebo (n=9) groups, raising the question of the causal contribution of the underlying condition. J. Guevara-Aguirre, *et al.* (1995) at Tab 5.

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patients in Tercica's studies (as presented in a poster at the 2004 Endocrine Society Meeting) with the rates in previous publications on eight of the same subjects.[12] Petition at 10. Out of a total of three cases of intracranial hypertension, two occurred in the eight-patient subset. These numbers are simply too low to draw any scientifically valid conclusions. Moreover, the two initial cases of intracranial hypertension occurred in a pair of twins with a pre-existing condition of communicating hydrocephalus, whose intracranial hypertension resolved spontaneously despite continued rhIGF-1 therapy.[13] The combined rate of intracranial hypertension in the entire study (now, three cases in 71 patients) also is consistent with the reports in the published literature.[14]

With regard to the rate of tonsillectomy, the rate reported by Tercica from its clinical studies (approximately 10%) is consistent with the rates seen in the published literature.[15] Based on this rate, approximately 0.8 cases would be expected in the eight-patient subset. Tercica believes that an occurrence of two cases in the eight-patient subset is consistent with this expected rate.

This same conclusion applies to all of the adverse event rates referenced by Insmed in the petition. Petition at 8-12. The rates quoted by Insmed and those developed and reported from Tercica's clinical studies are entirely consistent. This is particularly so when taking into consideration the limitations of comparing adverse event rates across small studies conducted in different patient populations, with different routes of administration, and with different lengths of follow-up.

Insmed also cites a 1993 letter to the editor of the *New England Journal of Medicine* that reported cases of benign intracranial hypertension primarily with growth hormone treatment, but also with IGF-1 therapy. Petition at 12. The authors, however, do not reach a conclusion on the magnitude of the risk of intracranial hypertension. Rather, they recommend "ophthalmologic

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12 P.F. Backeljauw, *et al.*, *Therapy for 6.5-7.5 Years with Recombinant Insulin-Like Growth Factor I in Children with Growth Hormone Insensitivity Syndrome: A Clinical Research Center Study*, J. CLIN. ENDOCRINOL. METAB. 86(4): 1504-1510 (2001), attached at Tab 9; P.F. Backeljauw, *et al.*, *Prolonged Treatment with Recombinant Insulin-Like Growth Factor-I in Children with Growth Hormone Insensitivity Syndrome – A Clinical Research Center Study*, J. CLIN. ENDOCRINOL. METAB. 81(9): 3312-7 (1996), attached at Tab 10.

13 P.F. Backeljauw, *et al.* (1996) at Tab 10.

14 C. Azcona, *et al.* (1999) at Tab 3; J. Guevara-Aguirre, *et al.* (1995) at Tab 5.

15 M.B. Ranke, *et al.* (1995) at Tab 4.

examinations during the initial months of therapy for patients receiving growth hormone or insulin-like growth factor I, particularly if they report headaches or visual changes."[16] Today, twelve years after this letter to the editor, intracranial hypertension is accepted as an infrequent, non-life-threatening side effect of growth therapies, including growth hormone and IGF-1. Pediatric endocrinologists routinely evaluate children who complain of headache, nausea and/or vomiting with ophthalmologic examinations to rule out intracranial hypertension. This letter therefore does not support Insmed's assertion that Increlex™ therapy presents an unacceptable increased risk of adverse events.

As for the 1994 letter to the editor of *Annals of Internal Medicine*, Insmed misleads by omitting the fact that nine out of ten of the reported cases of syncope occurred with intravenous use of rhIGF-1. Petition at 12. Furthermore, the letter itself notes that, after an FDA recommendation to avoid intravenous injections or infusions of rhIGF-1, no further reports of syncope were received.[17] Again, this letter to the editor does not in any way support Insmed's conclusions about the safety profile of Increlex™.

Finally, Insmed points to a poster presented at the 2005 Endocrine Society Meeting, in which Tercica reported immunogenicity data on 22 (31%) of 71 subjects studied. To Insmed this implies that antibody response was not monitored by all physicians or that screening was not planned. Petition at 10. In fact, the data presented were obtained from a prospective two-year study that contained a formal assessment of antibody status in all but one of the subjects from the Genentech-sponsored Phase III studies.[18] This represents a rigorous evaluation of the antibody response to rhIGF-1 therapy.[19]

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16 S. Malozowski, *et al.*, *Growth hormone, insulin-like growth factor I, and benign intracranial hypertension* [letter], N. ENGL. J. MED. 329(9): 665-666, 666 (Aug. 6, 1993), attached at Tab 11.

17 S. Malozowski and B. Sadel, *Risks and benefits of insulin-like growth factor* [letter], ANN. INT. MED. 121(7): 549-550, 549 (Oct. 1, 1994), attached at Tab 12.

18 Tercica Press Release (June 6, 2005), attached at Tab 13. Antibody assessments were conducted for 23 subjects, but the test on one subject was performed outside the defined time window for inclusion in the analysis.

19 Insmed also argues that data presented in Tercica's scientific posters reveal incomplete follow-up or a larger number of study drop-outs than reported by Tercica. Petition at 8-10. Specifically, Insmed states that a poster presented at the 2004 Endocrine Society Meeting reports third-year efficacy results for only 24 of 65 patients and suggests that there was incomplete follow-up or under-reported drop-outs. This is not the case. For this poster, annual height velocities were computed using heights measured on or about the anniversary of each subjects' initiation of treatment. Year 3 height velocities were not included in this poster unless the height was measured close to the end of year 3. Therefore, the number of

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C. The Studied Population Supports the Indication

Insmed asserts that data used to support the Increlex™ NDA were obtained from subjects with GHIS, rather than from those with severe Primary IGFD. According to Insmed, data obtained from GHIS patients cannot be used to support approval of Increlex™ for patients with severe Primary IGFD. Petition at 14-15. Insmed offers no scientific or medical evidence to advance this point; rather, Insmed relies solely on a single public statement from Tercica. Once again, under examination, Insmed has offered yet another empty argument.

The Tercica statement presented by Insmed (Petition at 14) relates primarily to changes in the evolving nomenclature of growth hormone sensitivity disorders – from growth hormone insensitivity syndrome or GHIS, to IGF deficiency or IGFD, including pediatric IGFD and, more recently, Primary IGFD and severe Primary IGFD. The statement quoted by Insmed recognizes that the early Genentech studies were characterized as GHIS studies, or enrolled GHIS patients, but that under more recent nomenclature, different terminology may be more appropriate.

More specifically, the nomenclature used to describe the heterogeneous family of GHIS and related growth disorders has evolved considerably since the Increlex™ development program began over a decade ago. For example, we now know that the state of a child's GH insensitivity does not predict his or her response to rhIGF-1. Researchers have discovered a variety of mutations – in the IGF-1 gene, IGF-1 receptor, GH receptor, intracellular signaling molecules, and IGF binding protein system – in children with short stature.[20] Some of these children are GH insensitive, but have normal or high blood IGF-1 concentrations. Others may have an inactive IGF-1 protein.

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subjects treated for at least three years exceeded the number of subjects with defined year 3 height velocities. In Study 1419, per agreement with FDA, we used interpolation of heights between dates before and after anniversary dates. Thus, Study 1419 includes data from more subjects at various time points.

Insmed also claims that this poster may under-report study withdrawals. Petition at 9. According to the poster, 11 out of 65 patients had completed or withdrawn from the study. Hence, 54 subjects remained. Of these 54, 12 subjects had height velocities and height standard deviation data for year 8 of treatment; thus year 8 efficacy data was reported for these 12 subjects. Data for the remaining subjects were not reported because the study is on-going, and the majority of subjects have been in the study for less than eight years.

[20] *See, e.g*, H.M. Domene, *et al.*, *Deficiency of the Circulating Insulin-like Growth Factor System Associated with Inactivation of the Acid-labile Subunit Gene*, N. ENGL. J. MED. 350(6): 570-7 (2004), attached at Tab 14; M.J. Abuzzahab, *et al.*, *IGF-I Receptor Mutations Resulting in Intrauterine and Postnatal Growth Retardation*, N. ENGL. J. MED. 349(23): 2211-22 (2003),

Until these recent clinical discoveries, made after the original Genentech orphan drug designation, the hormonal basis for short stature had been the subject of much debate in the scientific and medical literature. It is now accepted that the presence of IGF-1 is obligate for GH to be able to stimulate growth and that an isolated deficiency in IGF-1 can lead to short stature in humans.[21] Therefore, it is optimal to define children with short stature in terms of their IGF-1 deficiency rather than their likely sensitivity or insensitivity to GH therapy. Accordingly, the term "Primary IGF-1 Deficiency" was applied by leading IGF-1 researchers to describe the relevant disorder, and has since been accepted by the medical community.[22]

Tercica and DMEDP have discussed such developments in short stature nomenclature since early 2003. The indication, severe Primary IGFD, appropriately reflects the current understanding of the disease and the population studied in our Increlex™ program, including the early Genentech studies.

III. CONCLUSION

For the reasons discussed above, we respectfully request that the petition be denied. Insmed has failed to raise any issues, or present any evidence, that would justify a delay in the review of the NDA, let alone a denial of the application itself. Insmed's last-minute filing of a meritless citizen petition should not be condoned. For the benefit of patients, and for the integrity of the FDA review process, the petition should be denied on or before the user fee goal date of August 31, 2005.

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attached at Tab 15; E.M. Kofoed, *et al., Growth hormone insensitivity associated with a STAT5b mutation*, N. ENGL. J. MED. 349(12): 1139-47 (2003), attached at Tab 16; A.D. Goddard, *et al., Mutations of the Growth Hormone Receptor in Children with Idiopathic Short Stature: The Growth Hormone Insensitivity Study Group*, N. ENGL. J. MED. 333(17): 1093-8 (1995), attached at Tab 17.

21 *See, e.g.*, R.G. Rosenfeld, *Insulin-like Growth Factors and the Basis of Growth*, N. ENGL. J. MED. 349(23): 2184-6 (2003), attached at Tab 18.

22 *See, e.g.*, R.G. Rosenfeld and V. Hwa, *Toward a Molecular Basis for Idiopathic Short Stature*, J. CLIN. ENDOCRINOL. METAB. 89(3): 1066-7 (2004), attached at Tab 19; Z. Laron, *The Essential Role of IGF-I: Lessons from the Long-term Study and Treatment of Children and Adults with Laron Syndrome*, J. CLIN. ENDOCRINOL. METAB. 84(12): 4397-404 (1999), attached at Tab 20.

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Thank you for your attention to this matter and for devoting agency resources to these issues on such short notice.

Sincerely,

John A. Scarlett, M.D.
President and Chief Executive Officer
Tercica, Inc.

Attachments

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